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Microglial methylation “landscape” in human brain

Profiles differ across age, disease state, brain region

Philadelphia, December 28, 2021 – In the central nervous system, microglial cells play critical roles in development, aging, brain homeostasis, and pathology. Recent studies have shown variation in the gene-expression profile and phenotype of microglia across brain regions and between different age and disease states. But the molecular mechanisms that contribute to these transcriptomic changes in the human brain are not well understood. Now, [a new study](#) targets the methylation profile of microglia from human brain.

The study appears in [Biological Psychiatry](#), published by Elsevier.

Microglia, the brain’s own immune cells, were once thought of as a homogenous population that was either “activated” or “inactivated,” with either pro-inflammatory or neuroprotective effects. But the cells are now recognized to have a vast array of phenotypes depending on environmental conditions with myriad functional consequences. Microglia are increasingly appreciated as critical players in neurologic and psychiatric disorders.

Fatemeh Haghghi, PhD, senior author of the new work, said: “To address this gap in knowledge, we set out to characterize the DNA methylation landscape of human primary microglia cells and factors that contribute to variations in the microglia methylome.”

DNA methylation is the main form of epigenetic regulation, which determines the pattern of which genes are being turned “on” or “off” in various circumstances over time.

The researchers studied isolated microglia cells from post-mortem human brain tissue from 22 donors of various age, including 1 patient with schizophrenia, 13 with mood disorder, and 8 controls with no psychiatric disorder, taken from 4 brain regions. They analyzed the microglia using genome-scale methylation microarrays.

Unsurprisingly, microglia showed DNA methylation profiles that were distinct from other cells in the central nervous system. But less expected, said Haghghi, “we found that interindividual differences rather than brain region differences had a much larger effect on the DNA methylation variability.” In addition, an exploratory analysis showed differences in the methylation profile of microglia from brains of subjects with psychiatric disorders compared to controls.

John Krystal, MD, Editor of *Biological Psychiatry*, said of the work, “These promising data point to pathology of the microglia, key immune cells of the brain, in the biology of depression.”

Notes for editors

The article is "Contribution of age, brain region, mood disorder pathology, and interindividual factors on the methylome of human microglia," by Lot de Witte, Zhaoyu Wang, Gijsje Snijders, Natalia Mendeleev, Qingkun Liu, Marjolein Sneebouer, Marco Boks, Yongchao Ge, Fatemeh Haghighi (<https://doi.org/10.1016/j.biopsych.2021.10.020>). It appears as an Article in Press in *Biological Psychiatry*, published by [Elsevier](#).

Copies of this paper are available to credentialed journalists upon request; please contact Rhiannon Bugno at Biol.Psych@sobp.org or +1 254 522 9700. Journalists wishing to interview the authors may contact Fatemeh Haghighi at fatemeh.haghighi@mssm.edu.

The authors' affiliations and disclosures of financial and conflicts of interests are available in the article.

John H. Krystal, MD, is Chairman of the Department of Psychiatry at the Yale University School of Medicine, Chief of Psychiatry at Yale-New Haven Hospital, and a research psychiatrist at the VA Connecticut Healthcare System. His disclosures of financial and conflicts of interests are available [here](#).

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